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Evolving Erosive GERD Therapeutics: Insights into a Treatment Option with a Novel MOA

Announcer:

You're listening to *GI Insights* on ReachMD. This medical industry feature, titled "Evolving Erosive GERD Therapeutics: Insights on the First FDA-Approved PCAB," is sponsored by Phathom Pharmaceuticals.

Here's your host, Dr. Jennifer Caudle.

Dr. Caudle:

Although about 20% of the U.S. adult population is affected by gastroesophageal reflux disease, or GERD for short, we've been using the same approach to treat this condition for 30 years, until now. Welcome to *GI Insights* on ReachMD. I'm your host, Dr. Jennifer Caudle, and joining me today to discuss potassium competitive acid blockers, or PCABs, which feature a novel mechanism of action to suppress acid production, is Dr. Partha Nandi. He's a Gastroenterologist and a Clinical Associate Professor of Medicine at Michigan State University and the Chief Health Editor for WXYZ ABC Detroit. Dr. Nandi, it's great to have you with us.

Dr. Nandi:

Thank you for having me, Dr. Caudle.

Dr. Caudle:

So Dr. Nandi, why don't we begin by discussing some of the treatment challenges doctors may encounter when treating GERD.

Dr. Nandi:

Sure. So GERD is caused by the reflux of acidic gastric contents into the esophagus, which can lead to heartburn and regurgitation. Now, there are two types of GERD, Erosive and Non-Erosive. Erosive GERD, also known as Erosive Esophagitis, is characterized by esophageal erosions visible by endoscopy. Of those patients who have GERD, about 30% have Erosive GERD, while 70% have Non-Erosive GERD, also known as Non-Erosive gastroesophageal reflux disease. So if we zero in on Erosive GERD, it's broken down using the Los Angeles, or LA, grading system, which is based on erosion severity. About 30% of patients with Erosive GERD have moderate to severe disease, or LA grade C or D.

Now with that in mind, the challenge for healthcare providers treating Erosive GERD patients is actually getting these erosions to heal and then to stay healed. Treatment for Erosive GERD usually involves the use of acid suppressants such as proton pump inhibitors, which are also known as PPIs, but about 4 to 15% of patients fail to achieve complete healing after an initial 8-week course of PPI therapy. And for patients who do heal, between 15 and 41% relapse during 6 months of PPI maintenance therapy, and roughly 80% experience a recurrence within 6 months of discontinuing treatment.

Dr. Caudle:

You know, with that being said, why do you think it can be a challenge to heal and maintain healing of these erosions?

Dr. Nandi:

That's a great question, Dr. Caudle. One of the main challenges is suppressing gastric acid to a level that allows erosions to heal. Exposure to a pH below 4, it can reduce the ability of the esophagus to heal. And studies have shown that healing rates are correlated

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with the amount of time that the gastric pH is above 4 over the course of 24 hours. So we need to achieve and maintain a high degree of acid suppression for esophageal erosions to have the best chance of healing.

Another challenge is that patients aren't always adherent when it comes to taking their medication. And most PPIs, they should be taken 30 to 60 minutes before a meal to achieve maximum acid suppression, but many patients, they struggle to follow this guidance. In fact, a recent survey found that about half of patients with Erosive GERD were not fully adherent, and of those patients, almost 90% forgot to take their medication at least some of the time.

Dr. Caudle:

You know, with those challenges in mind, Dr. Nandi, let's turn our attention to the class of acid suppressants known as PCABs. Can you tell us more about the only FDA approved PCAB and its mechanism of action?

Dr. Nandi:

Absolutely. So VOQUEZNA, or vonoprazan, is the first PCAB approved in the U.S. Now, VOQUEZNA is indicated for the healing of all grades of Erosive Esophagitis, or Erosive GERD, and relief of heartburn associated with Erosive GERD in adults, in addition to the maintenance of healing of all grades of Erosive GERD and relief of heartburn associated with Erosive GERD in adults. It's now also approved for the relief of heartburn associated with Non-Erosive GERD in adults. 20 mg daily is the approved dose for the healing of Erosive GERD, while the approved dose for the maintenance of healing of Erosive GERD and Non-Erosive GERD is 10 mg once daily. As a PCAB, VOQUEZNA works by competitively inhibiting the binding of potassium to acid pumps, ultimately reducing the amount of gastric acid that's produced.

Before we dive into the details on VOQUEZNA, let's discuss some important safety information.

Announcer:

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

VOQUEZNA is contraindicated in patients with a known hypersensitivity to vonoprazan or any component of VOQUEZNA, or in patients receiving rilpivirine-containing products.

WARNINGS AND PRECAUTIONS

Presence of Gastric Malignancy: In adults, symptomatic response to therapy with VOQUEZNA does not preclude the presence of gastric malignancy. Consider additional follow-up and diagnostic testing in patients who have a suboptimal response or an early symptomatic relapse after completing treatment with VOQUEZNA. In older patients, also consider endoscopy.

Acute Tubulointerstitial Nephritis: Acute tubulointerstitial nephritis (TIN) has been reported with VOQUEZNA. If suspected, discontinue VOQUEZNA and evaluate patients with suspected acute TIN.

Please listen to additional important safety information for VOQUEZNA later in this program.

Dr. Nandi:

Now, there are several differences between VOQUEZNA and lansoprazole, a PPI, and I just want to highlight three of those differences here. Before I do, however, please note that the clinical significance of these mechanistic differences has not been established. First, VOQUEZNA has a half-life of 7.7 to 7.9 hours, compared to the 1.5 hours for lansoprazole. This long half-life for VOQUEZNA may enable it to provide durable acid suppression throughout the day.

Second, VOQUEZNA doesn't require acid for activation and can be taken with or without food. Whereas lansoprazole requires acid for activation and should be taken 30 to 60 minutes before a meal. And lastly, VOQUEZNA binds to acid pumps in a reversible, noncovalent manner, which may allow disengaged VOQUEZNA to bind to newly activated pumps. In contrast, lansoprazole binds to acid pumps in an irreversible, covalent manner.

Dr. Caudle:

Now, those are some interesting mechanistic differences, Dr. Nandi. So if we zero in on the level of acid suppression VOQUEZNA provides, what do we need to know about that?

Dr. Nandi:

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So the effects of VOQUEZNA on intragastric acidity were studied in a phase 1, open-label, crossover study with 44 healthy volunteers. Healthy volunteers were randomized to 7 days of vonoprazan 20 mg once daily, followed by lansoprazole 30 mg once daily, or the reverse, separated by a greater than or equal to 7-day washout. Subjects fasted and received study drug each morning on days 1 and 7 of each 7-day period, breakfast was held, and subjects received standardized meals, 4 and 9 hours post dose, and a snack 12 hours post dose.

In this study, VOQUEZNA was shown to provide rapid, potent, and durable acid suppression. Following a single 20-mg dose, VOQUEZNA suppressed acid quickly between 2 and 3 hours, and reached a pH above 4 within 4 hours. I'd like to note that the clinical significance of quantitative differences in mean intragastric pH or mean pH holding time ratio have not been established. With that said, VOQUEZNA demonstrated interesting data regarding the level of acid suppression.

On day 1, VOQUEZNA demonstrated potent acid suppression, achieving a mean intragastric pH of 4.6 compared to 2.8 for lansoprazole. And on day 7, VOQUEZNA achieved a mean intragastric pH of 5.9 versus 3.8 for lansoprazole. Additionally, VOQUEZNA maintained durable, continuous acid suppression over 24 hours. The study found that on day 1, VOQUEZNA maintained a pH above 4 for 62% of the day, versus 23% with lansoprazole. And by day 7, VOQUEZNA maintained a pH above 4 for 88% of the day, compared to 42% with lansoprazole.

Dr. Caudle:

You're listening to *GI Insights* on ReachMD and I'm your host Dr. Jennifer Caudle. Today I'm speaking with Dr. Partha Nandi about the potassium-competitive acid blocker, or PCAB, called VOQUEZNA (vonoprazan) for the treatment of Erosive GERD.

So Dr. Nandi, if we continue examining the data, how does VOQUEZNA do in terms of treating Erosive GERD? Is it able to completely heal erosions?

Dr. Nandi:

That's a great question, because ultimately, that's what we all want to know, right? How will this work in my practice. VOQUEZNA was studied in a phase 3, randomized, active-control, double-blind, two-phase study known as pHalcon-EE, which was conducted in the U.S. and Europe. In the first phase, VOQUEZNA 20 mg once daily was compared with lansoprazole 30 mg once daily in the healing of Erosive GERD. And patients were endoscopically evaluated at week 2, and if they were not healed, they were evaluated again at week 8.

Patients who were H. pylori positive or who had Barrett's esophagus and or definite dysplastic changes in the esophagus at baseline were excluded from the study.

The primary noninferiority endpoint for the healing phase was the percentage of patients with complete healing of Erosive GERD by week 8. And the patients who showed endoscopically confirmed healing at week 2 or week 8 were then rerandomized in the maintenance phase to receive either VOQUEZNA 10 mg once daily, or lansoprazole 15 mg once daily. The primary noninferiority endpoint in the maintenance phase was the percentage of patients who maintained complete healing at 24 weeks.

Now, in terms of the results, VOQUEZNA met the primary efficacy endpoint for the healing phase by demonstrating noninferiority to lansoprazole by week 8 in patients across all grades of Erosive GERD. 93% of VOQUEZNA patients achieved complete healing, compared to 85% of lansoprazole patients. This noninferiority analysis demonstrated a p-value of less than 0.0001.

Strong healing rates were also observed at week 2, with 74% of VOQUEZNA patients achieving healing, compared to 68% of patients in the lansoprazole arm. This week 2 endpoint, however, was not tested for statistical significance due to prespecified hierarchy and should not be interpreted as showing superiority.

Among patients with moderate to severe disease, defined as LA grade C or D, VOQUEZNA demonstrated superior healing rates at week 2. And in this population, 70% of VOQUEZNA patients achieved complete healing, compared with 53% of lansoprazole patients. The p-value for this superiority analysis was 0.0008.

Strong healing rates were also observed by week 8 for this patient group, with 92% of VOQUEZNA patients achieving healing, versus 72% of patients receiving lansoprazole. However, this week 8 endpoint was not tested for statistical significance due to prespecified hierarchy, and should not be interpreted as showing superiority. Now, as far as maintenance of healing, VOQUEZNA met the primary noninferiority endpoint in the maintenance phase across all grades of Erosive GERD, as 79% of VOQUEZNA patients achieved maintenance of healing at week 24, versus 72% of lansoprazole patients. This noninferiority analysis demonstrated a p-value of less than 0.0001.

A secondary endpoint, also demonstrated that VOQUEZNA achieved superior maintenance of healing rates at week 24 in patients with

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all grades of Erosive GERD with a p-value of 0.044. Lastly, VOQUEZNA demonstrated superior maintenance of healing rates with a p-value of 0.049 in patients with moderate to severe Erosive GERD at week 24, with 75% of VOQUEZNA treated patients achieving sustained healing, compared to 61% of lansoprazole treated patients.

Before we dive into safety data, let's hear some additional important safety information for VOQUEZNA.

Announcer:

IMPORTANT SAFETY INFORMATION *(continued)*

WARNINGS AND PRECAUTIONS *(continued)*

***Clostridioides difficile*-Associated Diarrhea:** Published observational studies suggest that proton pump inhibitors (PPIs) may be associated with an increased risk of Clostridioides difficile-associated diarrhea (CDAD), especially in hospitalized patients. VOQUEZNA may also increase the risk of CDAD. Consider CDAD in patients with diarrhea that does not improve. Use the shortest duration of VOQUEZNA appropriate to the condition being treated.

Bone Fracture: Several published observational studies suggest that PPI therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist, or spine, especially in patients receiving high dose (multiple daily doses) and long-term therapy (a year or longer). Bone fracture, including osteoporosis-related fracture, has also been reported with vonoprazan. Use the shortest duration of VOQUEZNA appropriate to the condition being treated. Patients at risk for osteoporosis-related fractures should be managed according to the established treatment guidelines.

Severe Cutaneous Adverse Reactions (SCAR): Severe cutaneous adverse reactions, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported with VOQUEZNA. Discontinue VOQUEZNA at the first signs or symptoms of SCAR or other signs of hypersensitivity and consider further evaluation.

Please listen to additional important safety information for VOQUEZNA later in this program.

Dr. Caudle:

Now, what about the safety profile? What were the findings there?

Dr. Nandi:

Happy to share the safety data. But first, please note that this clinical trial was not designed to support comparative adverse event claims for VOQUEZNA. Overall, the safety profile of VOQUEZNA was comparable with lansoprazole. The most common adverse event in the healing phase was gastritis reported in 3% of patients with VOQUEZNA versus 2% with lansoprazole. 2% of patients reported diarrhea with VOQUEZNA versus 3% with lansoprazole. Abdominal distension, abdominal pain, and nausea were reported in 2% of patients with VOQUEZNA versus 1% with lansoprazole.

Now, in the maintenance phase, the most common adverse event was gastritis, reported in 6% of patients with VOQUEZNA versus 3% with lansoprazole. 4% of patients reported abdominal pain with VOQUEZNA versus 2% with lansoprazole. And 4% of patients reported dyspepsia with VOQUEZNA versus 3% with lansoprazole. Hypertension and urinary tract infection were reported in 3% of patients with VOQUEZNA versus 2% with lansoprazole.

Dr. Caudle:

Thanks for breaking down all of that data for us, Dr. Nandi.

Now, we're almost out of time for today, so I just want to close by asking you about your clinical perspective on VOQUEZNA. What motivates you to want to use VOQUEZNA for your adult patients with Erosive GERD?

Dr. Nandi:

From my vantage point, I am excited about a medication that has demonstrated complete healing in over 90% of clinical trial patients by week 8. For me, that's pretty reassuring. I'm also excited about a treatment option that can be taken once a day without regard to meals. I think this will take some of the burden off my patients who have challenges with mealtime dosing. And now that VOQUEZNA is approved for the relief of heartburn associated with Non-Erosive GERD, I have a treatment option for another class of patients.

Before we close, let's discuss some additional important safety information.

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IMPORTANT SAFETY INFORMATION *(continued)*

WARNINGS AND PRECAUTIONS *(continued)*

Vitamin B12 (Cobalamin) Deficiency: Long-term use of acid-suppressing drugs can lead to malabsorption of Vitamin B12 caused by hypo- or achlorhydria. Vitamin B12 deficiency has been reported postmarketing with vonoprazan. If clinical symptoms consistent with vitamin B12 deficiency are observed in patients treated with VOQUEZNA, consider further workup.

Hypomagnesemia and Mineral Metabolism: Hypomagnesemia has been reported postmarketing with vonoprazan. Hypomagnesemia may lead to hypocalcemia and/or hypokalemia and may exacerbate underlying hypocalcemia in at-risk patients.

Consider monitoring magnesium levels prior to initiation of VOQUEZNA and periodically in patients expected to be on prolonged treatment, in patients taking drugs that may have increased toxicity in the presence of hypomagnesemia or drugs that may cause hypomagnesemia. Treatment of hypomagnesemia may require magnesium replacement and discontinuation of VOQUEZNA.

Consider monitoring magnesium and calcium levels prior to initiation of VOQUEZNA and periodically while on treatment in patients with a preexisting risk of hypocalcemia. Supplement with magnesium and/or calcium, as necessary. If hypocalcemia is refractory to treatment, consider discontinuing VOQUEZNA.

Interactions with Diagnostic Investigations for Neuroendocrine Tumors: Serum chromogranin A (CgA) levels increase secondary to drug-induced decreases in gastric acidity. The increased CgA level may cause false positive results in diagnostic investigations for neuroendocrine tumors. Temporarily discontinue VOQUEZNA treatment at least 4 weeks before assessing CgA levels and consider repeating the test if initial CgA levels are high.

Fundic Gland Polyps: Use of VOQUEZNA is associated with a risk of fundic gland polyps that increases with long-term use, especially beyond one year. Fundic gland polyps have been reported with vonoprazan in clinical trials and during postmarketing use with PPIs. Most patients who developed fundic gland polyps were asymptomatic and fundic gland polyps were identified incidentally on endoscopy. Use the shortest duration of VOQUEZNA appropriate to the condition being treated.

ADVERSE REACTIONS:

Healing of Erosive GERD: The most common adverse reactions (≥2% of patients in the VOQUEZNA arm) include gastritis (3%), diarrhea (2%), abdominal distention (2%), abdominal pain (2%), and nausea (2%).

Maintenance of Healed Erosive GERD: The most common adverse reactions (≥3% of patients in the VOQUEZNA arm) include gastritis (6%), abdominal pain (4%), dyspepsia (4%), hypertension (3%), and urinary tract infection (3%).

Relief of Heartburn Associated with Non-Erosive GERD: The most common adverse reactions (≥2% of patients in the VOQUEZNA arm) include abdominal pain (2%), constipation (2%), diarrhea (2%), nausea (2%), and urinary tract infection (2%).

DRUG INTERACTIONS

VOQUEZNA has the potential for clinically important drug interactions, including interactions with drugs dependent on gastric pH for absorption, drugs that are substrates for certain CYP enzymes, and some diagnostic tests. Avoid concomitant use of VOQUEZNA with atazanavir or nelfinavir. See full Prescribing Information for more details about important drug interactions. Consult the labeling of concomitantly used drugs to obtain further information about interactions with vonoprazan.

USE IN SPECIFIC POPULATIONS

Lactation: Breastfeeding is not recommended during treatment. Because of the potential risk of adverse liver effects shown in animal studies with vonoprazan, advise patients not to breastfeed during treatment with VOQUEZNA.

Renal Impairment: For the healing of Erosive GERD, dosage reduction is recommended in patients with severe renal impairment (eGFR < 30 mL/min).

Hepatic Impairment: For the healing of Erosive GERD, dosage reduction is recommended in patients with moderate to severe hepatic impairment (Child-Pugh Class B and C).

You are encouraged to report suspected adverse reactions by contacting Phathom Pharmaceuticals at 1-888-775-PHAT (7428) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Please see full Prescribing Information for VOQUEZNA at www.VoqueznaPro.com.

Dr. Caudle:

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And as that brings us to the end of our program, I'd like to thank my guest, Dr. Partha Nandi, for chatting with us about VOQUEZNA, which is the first FDA approved PCAB for the treatment of Erosive GERD and the relief of heartburn associated with Non-Erosive GERD in adults. Dr. Nandi, it was great speaking with you today.

Dr. Nandi:

Thank you. It's been a pleasure!

Dr. Caudle:

And for ReachMD, I'm Dr. Jennifer Caudle. Thanks for listening!

Announcer:

This medical industry feature was sponsored by Phathom Pharmaceuticals. If you missed any part of this discussion or to find others in this series, visit *GI Insights* on ReachMD dot com, where you can Be Part of the Knowledge. Thanks for listening!

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